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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Case No. 02-090-B

In re Application of:

Bakthavatchalam *et al.*

Serial No.: 09/910,442

Filed: July 20, 2001

For: Capsaicin Receptor Ligands

Before the Examiner:
Kahsay Habte

Art Unit: 1624

RESPONSE TO THE OFFICE ACTION
MAILED MARCH 4, 2003

Commissioner for Patents
Alexandria, VA 22313

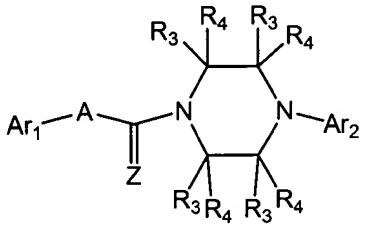
Dear Sir:

Responsive to the Office Action mailed March 4, 2003, Applicants respectfully request the Examiner to reconsider the above-identified patent application in view of the following Amendments and Remarks.

AMENDMENTS

1-3. (Cancelled)

4. (Currently Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, NR_A, $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen and alkyl;

Z is oxygen or sulfur;

each R_3 and R_4 is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted

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alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted $-S(O)_nNHalkyl$; optionally substituted $-S(O)_nN(alkyl)(alkyl)$; optionally substituted $-NHC(=O)alkyl$; optionally substituted $-NC(=O)(alkyl)(alkyl)$; optionally substituted $-NHS(O)_nalkyl$; optionally substituted $-NS(O)_n(alkyl)(alkyl)$; optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a R_3 or R_4 not attached to the same carbon to form an optionally substituted aryl ring, a

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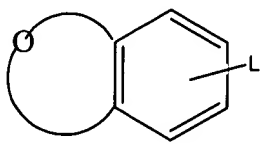
saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms selected from N, O, and S;

Ar_1 is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R_5; and

(b) bicyclic oxygen-containing groups of the formula:



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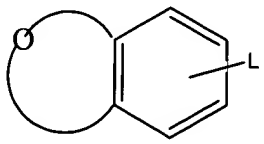
optionally mono-, di-, or trisubstituted with R_5, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

Ar_2 is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, [pyrazinyl,] benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R_5; and

(b) bicyclic oxygen-containing groups of the formula:



optionally mono-, di-, or trisubstituted with R_5, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing

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ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R_5 is independently selected at each occurrence from the group consisting of halogen, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy and Y;

C1

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-S(O)_n(C_{1-4}alkyl)$, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-4}alkyl_1)(C_{1-4}alkyl_2)$ where $alkyl_1$ and $alkyl_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, -O-, $-S(O)_n-$, -NH-, $-NR_8-$, -C(=O)-, -C(=O)O-, -C(=O)NH-, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, NHC(=O)-, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

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R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_n$(alkyl), $-S(O)_n$(alkyl), $-S(O)_nNH$(alkyl), $-S(O)_nN(alkyl_3)(alkyl_4)$ where $alkyl_3$ and $alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo,

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hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

C1 26. (Previously Amended) A compound or salt according to Claim 1, wherein:

R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen and C_{1-6}alkyl;

each R_3 and R_4 is independently

(a) chosen from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6; C_{2-6}alkynyl substituted with 0-2 R_6; C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y; or

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(b) joined to a R_3 or R_4 not attached to the same carbon to form an aryl ring substituted with 0-3 R_6, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R_6, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R_6 and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

C1

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(C_{1-4}alkyl), -N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl), -NHS(O)$_n$(C_{1-4}alkyl), -S(O)$_n$(C_{1-4}alkyl), -S(O)$_n$NH(C_{1-4}alkyl), -S(O)$_n$N(C_{1-4}alkyl$_3$)(C_{1-4}alkyl$_4$) where C_{1-4}alkyl$_3$

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and $C_{1-4}alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y'; and

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S.

36. (Original) A compound or salt according to Claim 14, wherein Z is oxygen.

7. (Cancelled)

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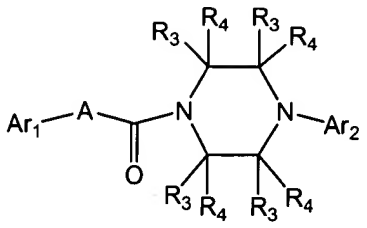
48. (Currently Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_B', $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen or alkyl;

each R_3 and R_4 is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted $-S(O)_nNHalkyl$; optionally substituted $-S(O)_nN(alkyl)(alkyl)$; optionally substituted -NHC(=O)alkyl; optionally

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substituted -NC(=O)(alkyl)(alkyl); optionally substituted -NHS(O)$_n$alkyl; optionally substituted -NS(O)$_n$(alkyl)(alkyl); optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a R_3 or R_4 not attached to the same carbon to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

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Ar_1 [and Ar_2 are independently] is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl; wherein Ar_1 is optionally mono-, di-, or trisubstituted with R_5, and Ar_2 is optionally mono-, di-, or trisubstituted with R_9;

C1

Ar_2 is selected from the group consisting of:

cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl; wherein Ar_1 is optionally

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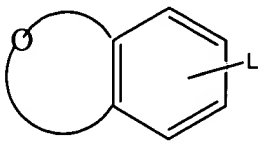
mono-, di-, or trisubstituted with R_5, and Ar_2 is optionally mono-, di-, or trisubstituted with R_9; and

(b) groups of the formula:



optionally mono-, di-, or trisubstituted with R_5, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R_5 is independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6, alkenyl substituted with 0-2 R_6, alkynyl substituted with 0-2 R_6, alkoxy and Y;

R_9 is independently selected at each occurrence from the group consisting of nitro, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6, alkenyl substituted with 0-2 R_6, alkynyl substituted with 0-2 R_6, alkoxy substituted with 0-2 R_6, and Y;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, alkyl,

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alkoxy, $-S(O)_n$(alkyl), haloalkyl, haloalkoxy, CO(alkyl), CONH(alkyl), CON($alkyl_1$)($alkyl_2$) where $alkyl_1$ and $alkyl_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, -O-, $-S(O)_n-$, -NH-, $-NR_8-$, -C(=O)-, -C(=O)O-, -C(=O)NH-, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, NHC(=O)-, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl),

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-NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_n(alkyl)$, $-S(O)_n(alkyl)$, $-S(O)_nNH(alkyl)$, $-S(O)_nN(alkyl_3)(alkyl_4)$ where $alkyl_3$ and $alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

59. (Previously Amended) A compound of the formula:

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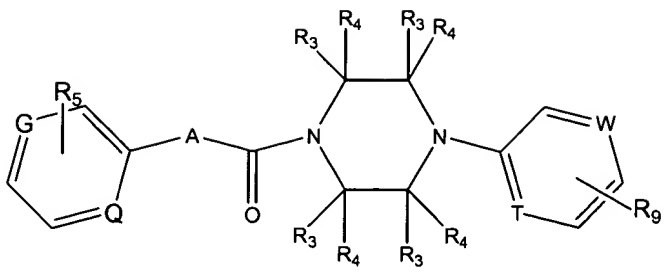

or a pharmaceutically acceptable salt thereof, wherein:

G, Q, T, and W are the same or different and are selected from the group consisting of N, CH, and CR_5, wherein T or W or both is N;

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_B', $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen and alkyl;

Z is oxygen or sulfur;

each R_3 and R_4 is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted C_{1-6}alkyl; optionally substituted C_{2-6}alkenyl; optionally substituted C_{2-6}alkynyl; optionally substituted C_{1-6}alkoxy; optionally substituted mono or di(C_{1-6})alkylamino; optionally substituted C_{1-6}alkylthio; optionally substituted C_{1-6}alkyl ketone; optionally substituted C_{1-6}alkylester; optionally substituted C_{1-}

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$_6$alkylsulfinyl; optionally substituted C_{1-6}alkylsulfonyl; optionally substituted mono- or di(C_{1-6})alkylcarboxamide; optionally substituted -S(O)$_n$NH C_{1-6}alkyl; optionally substituted -S(O)$_n$N(C_{1-6}alkyl)(C_{1-6}alkyl); optionally substituted -NHC(=O) C_{1-6}alkyl; optionally substituted -NC(=O)(C_{1-6}alkyl)(C_{1-6}alkyl); optionally substituted -NHS(O)$_n$$C_{1-6}$alkyl; optionally substituted -NS(O)$_n$(C_{1-6}alkyl)(C_{1-6}alkyl); optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a R_3 or R_4 not attached to the same carbon to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is

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optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

R_5 represents 1 to 3 substituents independently selected at each occurrence from the group consisting of cyano, hydroxy, amino, C_{3-6} alkyl substituted with 0-2 R_6, C_{2-6} alkenyl substituted with 0-2 R_6, C_{2-6} alkynyl substituted with 0-2 R_6, C_{3-6} alkoxy, $-NH(C_{1-6}alkyl)$ substituted with 0-2 R_6, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y;

R_9 represents 0 to 3 substituents independently selected at each occurrence from the group consisting of halogen, nitro, $halo(C_{1-6})alkyl$, $halo(C_{1-6})alkoxy$, hydroxy, amino, $C_{1-6}alkyl$ substituted with 0-2 R_6, $C_{2-6}alkenyl$ substituted with 0-2 R_6, $C_{2-6}alkynyl$ substituted with 0-2 R_6, $C_{1-6}alkoxy$ substituted with 0-2 R_6, and Y;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-S(O)_n(C_{1-4}alkyl)$, $halo(C_{1-4})alkyl$, $halo(C_{1-4})alkoxy$, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-}$

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$_4$alkyl$_1$)(C_{1-4}alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, $-O(C_{1-4}alkyl)$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NHS(O)_n(C_{1-4}alkyl)$, $-S(O)_n(C_{1-}$

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$_4$alkyl), $-S(O)_nNH(C_{1-4}alkyl)$, $-S(O)_nN(C_{1-4}alkyl_3)(C_{1-4}alkyl_4)$ where $C_{1-4}alkyl_3$ and $C_{1-4}alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

10. (Original) A compound according to Claim 9, which is 4-(3-Chloro-2-pyridinyl)-N-[4(isopropyl)phenyl]-2-

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methylthio-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

11. (Original) A compound according to Claim 5, wherein R_3 and R_4 are independently selected at each occurrence from the group consisting of hydrogen and C_{1-6} alkyl.

12. (Original) A compound according to Claim 11, wherein G and Q are selected from the group consisting of CH and CR_5.

13. (Original) A compound according to Claim 11, wherein G , Q, and W are independently selected at each occurrence from the group consisting of CH and CR_5; and T is N.

14. (Original) A compound according to Claim 13 wherein R_3 and R_4 are hydrogen; and A is selected from the group consisting of NH, -CH=CH-, and $-CH_2NH-$.

15. (Original) A compound or salt according to Claim 14, wherein R_6 is independently selected at each occurrence

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from the group consisting of halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, -NH(C_{1-4}alkyl), and -N(C_{1-4} alkyl)(C_{1-4} alkyl).

16. (Original) A compound according to Claim 10, which is 4-(3-Trifluoromethyl-2-pyridinyl)-N-(3-methoxy-4-hydroxyphenylmethyl)-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

17. (Original) A compound according to Claim 10, which is 4-(3-Nitro-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

18. (Original) A compound according to Claim 10, which is 4-(3-Trifluoromethyl-2-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

19. (Original) A compound according to Claim 10, which is 4-(3-Methyl-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

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16 10

20. (Original) A compound according to Claim 14, which is 4-(3-Methyl-2-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

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21. (Original) A compound according to Claim 14, which is 4-(3-Chloro-5-trifluoromethyl-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

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22. (Original) A compound according to Claim 14, which is 4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

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23. (Original) A compound according to Claim 14, which is 4-(3,5-Dichloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

NE was cancelled Amd 13

24. (Original) A compound according to claim 13, which is 4-(3-Cyano-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-

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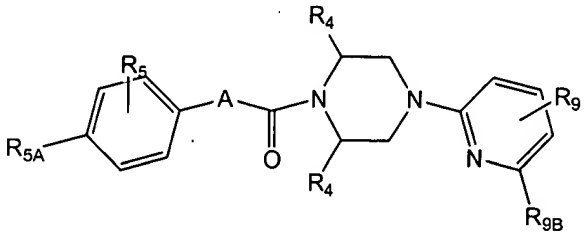
piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

25. (Original) The compound according to claim 13, which is 4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-2-methyl-1-piperazinecarboxamide.

26. (Previously Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and CH_2NH;

R_4 is independently chosen from hydrogen and C_{1-4} alkyl;

R_5 represents 0 to 2 substituents independently chosen at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, and -N(C_{1-6}alkyl)(C_{1-6}alkyl)

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where each C_{1-6}alkyl is independently substituted with 0-2 R_6;

R_9 represents 0 to 2 substituents and is independently chosen at each occurrence from the group consisting of halogen, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, and C_{1-6}alkoxy substituted with 0-2 R_6;

R_{5A} is independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), and -N(C_{1-6} alkyl)(C_{1-6} alkyl);

R_{9B} is independently selected from the group consisting of halogen, nitro, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R_6 is independently selected at each occurrence the group consisting of halogen, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -NH(C_{1-4} alkyl), and -N(C_{1-4} alkyl)(C_{1-4} alkyl).

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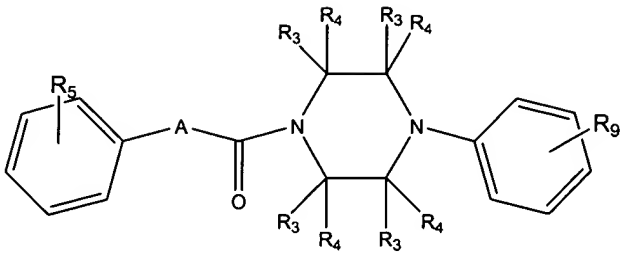
27. (Previously Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of a single bond, S, NR_A, NR_ACHR_B, CHR_BNR_A, $-CR_A=CR_B-$, and C_3H_4; where R_A and R_B are independently selected at each occurrence from the group consisting of hydrogen and alkyl;

each R_3 and R_4 is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted $-S(O)_nNHalkyl$; optionally substituted $-S(O)_nN(alkyl)(alkyl)$;

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optionally substituted -NHC(=O)alkyl; optionally substituted -NC(=O)(alkyl)(alkyl); optionally substituted -NHS(O)$_n$alkyl; optionally substituted -NS(O)$_n$(alkyl)(alkyl); optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a R_3 or R_4 not attached to the same carbon to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally

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substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

R_5 represents 0-3 substituents independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, C_{2-6} alkenyl substituted with 0-2 R_6, and C_{2-6} alkynyl substituted with 0-2 R_6;

R_9 represents 0-3 substituents independently selected at each occurrence from the group consisting of bromo, haloalkyl, haloalkoxy, hydroxy, C_{2-6} alkyl substituted with 0-2 R_6, C_{2-6} alkenyl substituted with 0-2 R_6, C_{2-6} alkynyl substituted with 0-2 R_6, and C_{2-6} alkoxy;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, alkyl, alkoxy, $-S(O)_n(alkyl)$, haloalkyl, haloalkoxy, $CO(alkyl)$, $CONH(alkyl)$, $CON(alkyl_1)(alkyl_2)$ where $alkyl_1$ and $alkyl_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$,

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$-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

R_7 and R_8 are independently selected at each occurrence from straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 3 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 3 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_n$(alkyl), $-S(O)_n$(alkyl), $-S(O)_nNH$(alkyl), $-S(O)_nN(alkyl_3)(alkyl_4)$ where $alkyl_3$ and $alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more

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substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

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28. (Original) A compound or salt according to Claim 27 in which R_3 and R_4 are independently selected at each occurrence from the group consisting of hydrogen and C_{1-6} alkyl.

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29. (Original) A compound or salt according to claim 27, wherein A is selected from the group consisting of NH, -CH=CH-, and CH_2NH; R_3 is hydrogen and R_4 is independently chosen at each occurrence from hydrogen and methyl; and R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, -NH(C_{1-4} alkyl), and -N(C_{1-4} alkyl)(C_{1-4} alkyl).

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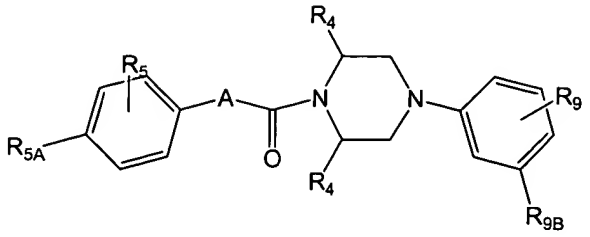
25 30. (Previously Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and CH_2NH;

R_4 is independently selected at each occurrence from hydrogen and C_{1-4}alkyl;

R_5 represents 0 to 2 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, amino, C_{2-6}alkenyl substituted with 0-2 R_6, and C_{2-6}alkynyl substituted with 0-2 R_6;

R_9 represents 0 to 2 substituents and is independently selected at each occurrence from the group consisting of halogen, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, and C_{1-6}alkoxy substituted with 0-2 R_6;

R_{5A} is independently selected from the group consisting of halogen, cyano, nitro, trifluoromethyl,

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trifluoromethoxy, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), and -N(C_{1-6} alkyl)(C_1-C_6 alkyl);

R_{9B} is independently selected from the group consisting of trifluoromethoxy, hydroxy, C_{2-6} alkyl, and C_{2-6} alkoxy; and

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, C_{1-4} alkyl, and C_{1-4} alkoxy.

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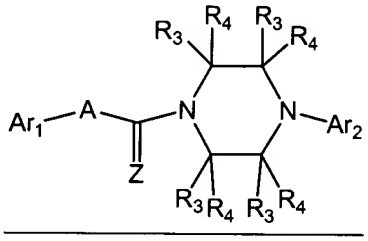
31. (Previously Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein the compound or pharmaceutically acceptable salt thereof exhibits an EC50 or K_i of 1 micromolar or less in a standard assay of capsaicin receptor mediated calcium mobilization; and wherein

A is absent or is selected from the group consisting of O, S, NR_A, $NR_ACR_BR_B'$, CR_B $R_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen and C_{1-6} alkyl;

Z is oxygen or sulfur;

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each R_3 and R_4 is independently

(a) selected from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6; C_{2-6}alkynyl substituted with 0-2 R_6; C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y; or

(b) joined to a R_3 or R_4 not attached to the same carbon to form an aryl ring substituted with 0-3 R_6, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R_6, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R_6 and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

Ar_1 is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl,

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pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R_5; and

(b) bicyclic oxygen-containing groups of the formula:

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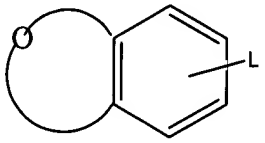

optionally mono-, di-, or trisubstituted with R_5, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

Ar_2 is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, [pyrazinyl,] benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl,

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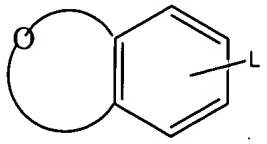
isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R_5; and

(b) bicyclic oxygen-containing groups of the formula:



optionally mono-, di-, or trisubstituted with R_5, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R_5 is independently selected at each occurrence from the group consisting of halogen, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy and Y;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-S(O)_n(C_{1-4}alkyl)$, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-}$

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$_4$alkyl$_1$)(C_{1-4}alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

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R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, $-O(C_{1-4}alkyl)$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NHS(O)_n(C_{1-4}alkyl)$, $-S(O)_n(C_{1-}$

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$_4$alkyl), -S(O)$_n$NH(C_{1-4}alkyl), -S(O)$_n$N(C_{1-4}alkyl$_3$)(C_{1-4}alkyl$_4$) where C_{1-4}alkyl$_3$ and C_{1-4}alkyl$_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

32. (Previously Amended) A compound of the Formula A, Formula B, Formula C, Formula D, Formula E, or Formula F:

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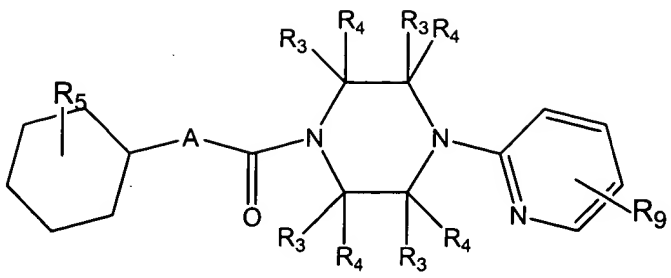
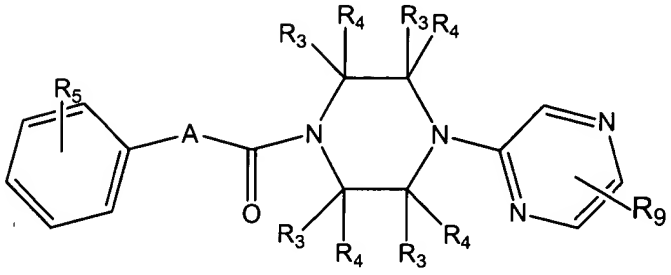
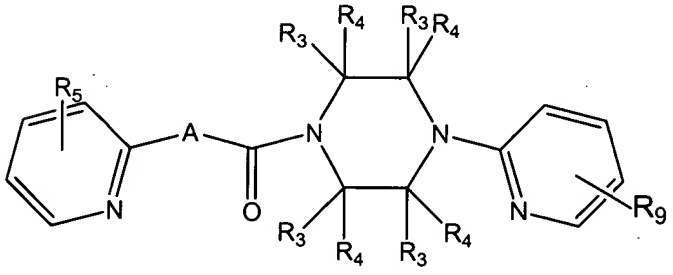


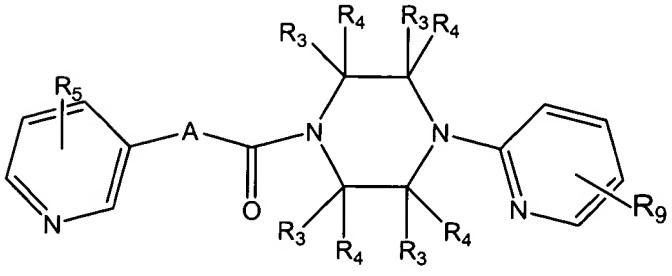
Formula A



Formula B



Formula C



Formula D

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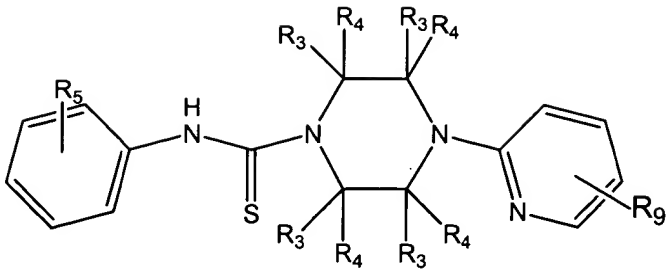
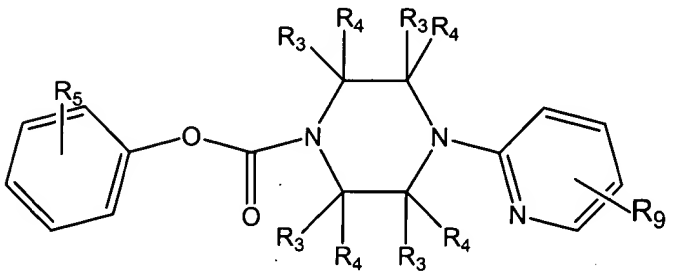


Formula E



Formula F

or a pharmaceutically acceptable salt of Formula A, Formula B, Formula C, Formula D, Formula E, or Formula F, wherein

A represents NH or O;

each R_3 and R_4 is independently

(a) selected from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6; C_{2-6}alkynyl substituted with 0-2 R_6; C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-

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$_6$alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6, -XR_7, and Y; or

(b) joined to a R_3 or R_4 not attached to the same carbon to form an aryl ring substituted with 0-3 R_6, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R_6, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R_6 and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

C1

R_5 represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6, -XR_7, and Y;

R_9 represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-}

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$_6$)alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, and Y;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-S(O)_n(C_{1-4}alkyl)$, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-4}alkyl_1)(C_{1-4}alkyl_2)$ where $alkyl_1$ and $alkyl_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

C1

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, -O-, $-S(O)_n-$, -NH-, $-NR_8-$, -C(=O)-, -C(=O)O-, -C(=O)NH-, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, NHC(=O)-, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon

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atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(C_{1-4}alkyl), -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), -NHC(O)(C_{1-4}alkyl), -N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl), -NHS(O)$_n$(C_{1-4}alkyl), -S(O)$_n$(C_{1-4}alkyl), -S(O)$_n$NH(C_{1-4}alkyl), -S(O)$_n$N(C_{1-4}alkyl$_3$)(C_{1-4}alkyl$_4$) where C_{1-4}alkyl$_3$ and C_{1-4}alkyl$_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio;

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wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

33. (Original) A compound or salt according to Claim 32, wherein A represents NH.

34. (Original) A compound or salt according to Claim 32, wherein:

A represents NH; and

R_3 and R_4 are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

35. (Original) A compound or salt according to Claim 32, wherein:

A represents NH;

R_3 represents hydrogen; and

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R_4 is independently chosen at each occurrence from hydrogen and C_{1-6} alkyl.

36. (Original) A compound or salt according to Claim 32, wherein:

A represents NH;

R_3 represents hydrogen; and

R_4 is independently chosen at each occurrence from hydrogen and methyl.

37. (Previously Amended) A compound or salt according to Claim 32, wherein:

A represents NH;

R_3 represents hydrogen;

R_4 is independently chosen at each occurrence from hydrogen and methyl; and

R_5 represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl; and

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R_9 represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, and C_{3-8} cycloalkyl.

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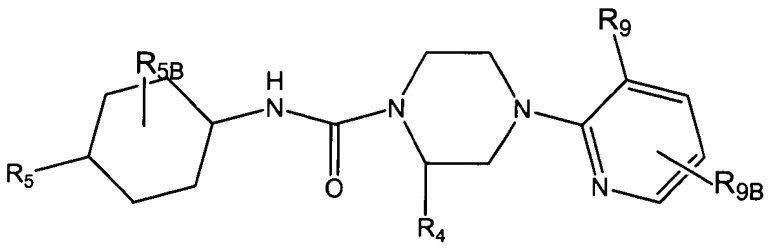
~~38~~. (Previously Amended) A compound or salt of the Formula A-1



Formula A-1

wherein

R_4 is hydrogen or methyl;

R_5 and R_9 are independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl; and

R_{5B} and R_{9B} each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl,

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halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3}alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

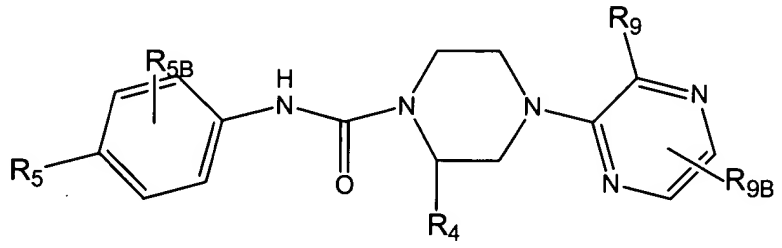
39. (Original) A compound or salt according to Claim 38, wherein:

R_5 is C_{3-6} alkyl; C_{3-6} alkoxy; halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, or C_{3-8} cycloalkyl;

R_9 is chloro or trifluoromethyl; and

R_{5B} and R_{9B} are hydrogen.

40. (Previously Amended) A compound or salt of Formula B-1:



Formula B-1

wherein

R_4 is hydrogen or methyl;

R_5 and R_9 are independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl,

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C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl; and

R_{5B} and R_{9B} each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3}alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

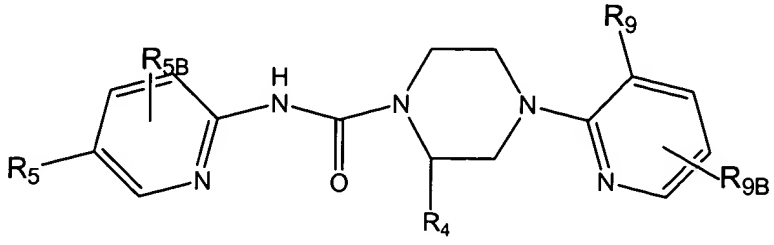
41. (Original) A compound or salt according to Claim 40, wherein:

R_5 is C_{3-6} alkyl; C_{3-6} alkoxy; halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, or C_{3-8} cycloalkyl;

R_9 is chloro or trifluoromethyl; and

R_{5B} and R_{9B} are hydrogen.

42. (Previously Amended) A compound or salt of Formula C-1:



Formula C-1

wherein:

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R_4 is hydrogen or methyl;

R_5 and R_9 are independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl; and

R_{5B} and R_{9B} each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3}alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

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43. (Original) A compound or salt according to Claim 37 42, wherein:

R_5 is C_{3-6} alkyl; C_{3-6} alkoxy; halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, or C_{3-8} cycloalkyl;

R_9 is chloro or trifluoromethyl; and

R_{5B} and R_{9B} are hydrogen.

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44. (Previously Amended) A compound or salt according to Claim 37 of Formula D-1:

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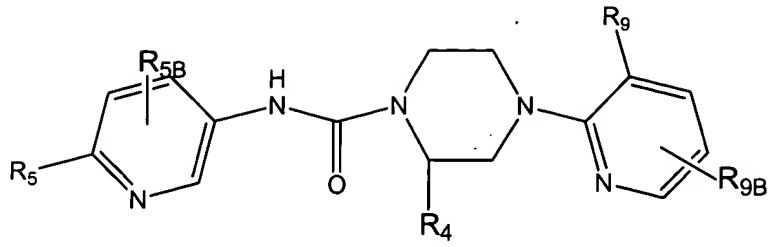

Formula D-1

wherein:

R_5 is selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl;

R_9 is selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, and C_{3-8} cycloalkyl; and

R_{5B} and R_{9B} each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3}alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

45. (Original) A compound or salt according to Claim 44, wherein:

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R_5 is C_{3-6} alkyl; C_{3-6} alkoxy; halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, or C_{3-8} cycloalkyl;

R_9 is chloro or trifluoromethyl; and

R_{5B} and R_{9B} are hydrogen.

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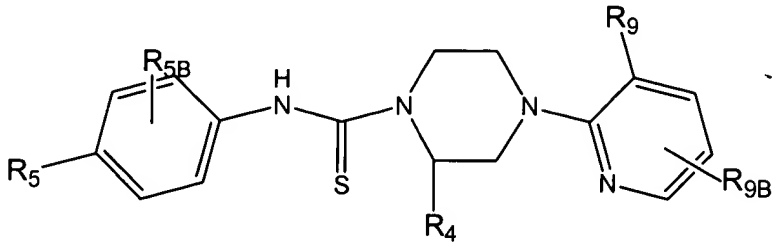
~~46~~. (Previously Amended) A compound or salt of Formula E-1:



Formula E-1

wherein:

R_4 is hydrogen or methyl;

R_5 and R_9 are independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl; and

R_{5B} and R_{9B} each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl,

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halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3}alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

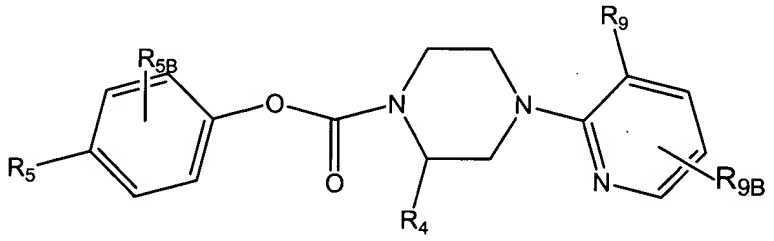
47. (Original) A compound or salt according to Claim 46, wherein:

R_5 is C_{3-6} alkyl; C_{3-6} alkoxy; halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, or C_{3-8} cycloalkyl;

R_9 is chloro or trifluoromethyl; and

R_{5B} and R_{9B} are hydrogen.

48. (Previously Amended) A compound of salt of Formula F-1:



Formula F-1

wherein:

R_4 is hydrogen or methyl;

R_5 and R_9 are independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl; and

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R_{5B} and R_{9B} each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3}alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

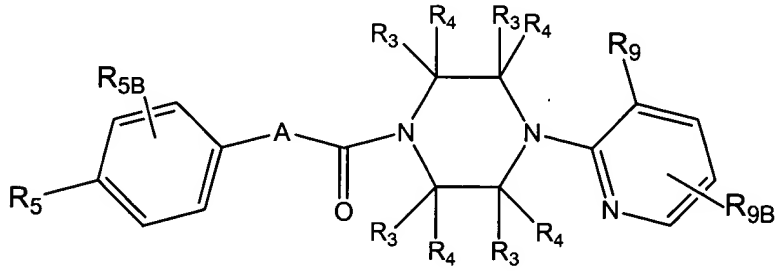
49. (Original) A compound or salt according to Claim 47, wherein:

R_5 is C_{3-6} alkyl; C_{3-6} alkoxy; halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, or C_{3-8} cycloalkyl;

R_9 is chloro or trifluoromethyl; and

R_{5B} and R_{9B} are hydrogen.

50. (Previously Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_B', $NR_ACR_BR_B'$, CR_B $R_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen and C_{1-6} alkyl;

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each R_3 and R_4 is independently

(a) selected from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6; C_{2-6}alkynyl substituted with 0-2 R_6; C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y; or

(b) joined to a R_3 or R_4 not attached to the same carbon to form an aryl ring substituted with 0-3 R_6, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R_6, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R_6 and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

R_5 is selected from the group consisting of bromo, fluoro, iodo, halo(C_{1-6})alkyl, halo(C_{3-6})alkoxy, C_{3-6}alkyl substituted with 0-3 R_6, C_{2-6}alkenyl substituted with 0-3 R_6, C_{2-6}alkynyl substituted with 0-3 R_6, C_{3-6}alkoxy, (C_{3-8}cycloalkyl)C_{1-4}alkyl, -NH(C_{1-6}alkyl) substituted

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with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is substituted with 0-2 R_6, Y, -(C=O)Y, -(CH_2)Y, and -(CH(CN))Y;

R_9 is selected from the group consisting of halogen, cyano, -N(SO_2C_{1-6}alkyl)(SO_2C_{1-6}alkyl), -SO_2NH_2, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, and C_{1-6}alkoxy substituted with 0-2 R_6;

R_{5B} represents from 0 to 2 substituents independently selected at each occurrence from the group consisting of

(a) halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, (C_{3-8}cycloalkyl)C_{1-4}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6, and Y; and

(b) groups that are joined to R_5 to form a C_{3-8}cycloalkyl group or a saturated heterocyclic ring or partially unsaturated heterocycle, each of which is optionally

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substituted by from 1 to 5 substituents independently chosen from cyano, halogen, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), halo(C_{1-4})alkyl, and halo(C_{1-4})alkoxy, wherein the saturated heterocyclic ring or partially unsaturated heterocycle contains from 4 to 8 ring atoms of which 1, 2, or 3 are heteroatoms independently selected from N, O, and S;

C1

R_{9B} represents from 0 to 2 substituents independently selected at each occurrence from halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, (C_{3-8}cycloalkyl)C_{1-4}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, and Y;

R_6 is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -S(O)$_n$(C_{1-4}alkyl), halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, CO(C_{1-4}alkyl), CONH(C_{1-4}alkyl), CON(C_{1-4}alkyl$_1$)(C_{1-4}alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3

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C

heteroatoms independently selected from N, O, and S, -XR_7, and Y;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_8-, -O-, -$S(O)_n$-, -NH-, -NR_8-, -C(=O)-, -C(=O)NH-, -$C(=O)NR_8$-, -$S(O)_nNH$-, -$S(O)_nNR_8$-, NHC(=O)-, -$NR_8C(=O)$-, -$NHS(O)_n$-, and -$NR_8S(O)_n$-;

C1

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -$O(C_{1-4}$alkyl), $NH(C_{1-4}$alkyl), -$N(C_{1-4}$alkyl)(C_{1-4}alkyl), -$NHC(O)(C_{1-4}$alkyl), -$N(C_{1-4}$alkyl)$C(O)(C_{1-4}$alkyl), -$NHS(O)_n(C_{1-4}$alkyl), -$S(O)_n(C_{1-4}$alkyl), -$S(O)_nNH(C_{1-4}$alkyl), -$S(O)_nN(C_{1-4}$alkyl$_3$)(C_{1-4}alkyl$_4$) where C_{1-4}alkyl$_3$ and C_{1-4}alkyl$_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5

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to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio;wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

51. (Original) A compound or salt according to Claim 50, wherein:

A is O or NR_A, wherein R_A is hydrogen or methyl.

52. (Original) A compound or salt according to Claim 50, wherein:

A is O or NR_A, wherein R_A is hydrogen or methyl; and

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R_3 and R_4 are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

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53. (Original) A compound or salt according to Claim 45 50, wherein:

A is O or NR_A, wherein R_A is hydrogen or methyl;

R_3 is hydrogen; and

R_4 is independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

49
54. (Original) A compound or salt according to Claim 45 50, wherein:

A is O or NR_A, wherein R_A is hydrogen or methyl;

R_3 is hydrogen; and

R_4 is independently chosen at each occurrence from hydrogen and C_{1-6}alkyl.

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55. (Original) A compound or salt according to Claim 50, wherein:

A is NR_A, wherein R_A is hydrogen or methyl;

R_3 is hydrogen; and

R_4 is independently chosen at each occurrence from hydrogen, halo(C_{1-3})alkyl, and C_{1-6}alkyl.

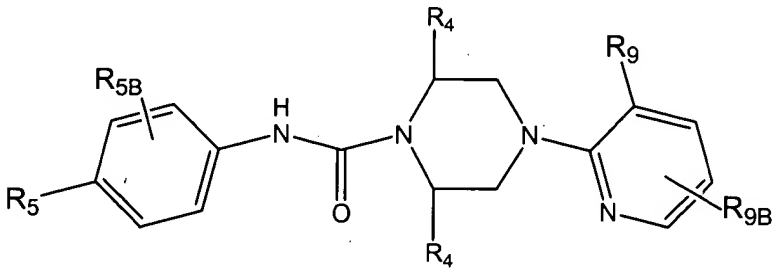
56. (Original) A compound or salt according to Claim 50, wherein:

A is NR_A, wherein R_A is hydrogen or methyl;

R_3 is hydrogen; and

R_4 is independently chosen at each occurrence from hydrogen and C_{1-4}alkyl.

57. (Original) A compound or salt according to Claim 50 of the Formula:



wherein:

R_4 is independently chosen at each occurrence from hydrogen and C_{1-4}alkyl.

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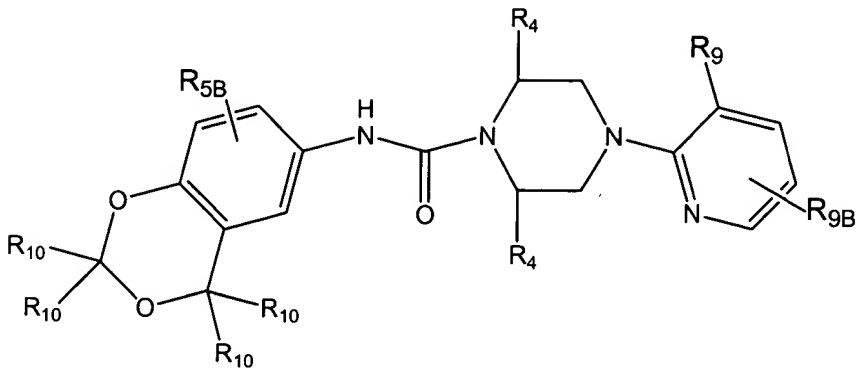
58. (Original) A compound or salt according to Claim 57 of the formula:



wherein

R_{5B} and R_{9B} are independently chosen from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{10} is independently chosen at each occurrence from hydrogen, halogen, and C_{1-4} alkyl.

59. (Previously Amended) A compound or salt according to Claim 58 wherein:

R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo(C_{1-3})alkyl, and C_{1-3}alkoxy.

60. (Original) A compound or salt according to Claim 57, wherein:

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R_{5B} and R_{9B} are independently chosen from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy.

61. (Original) A compound or salt according to Claim 57, wherein:

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, and C_{1-2}alkyl, and C_{1-2}alkoxy.

62. (Previously Amended) A compound or salt according to Claim 57, wherein:

R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo(C_{1-3})alkyl, and C_{1-3}alkoxy;

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, [and] C_{1-2}alkyl, and C_{1-2}alkoxy.

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63. (Previously Amended) A compound or salt according to Claim 57, wherein:

R_5 is selected from the group consisting of bromo, fluoro, iodo, halo(C_{1-6})alkyl, halo(C_{3-6})alkoxy, C_{3-6}alkyl substituted with 0-3 R_6, C_{2-6}alkenyl substituted with 0-3 R_6, Y, -(C=O)Y, -(CH_2)Y, and -(CH(CN))Y;

R_9 is selected from the group consisting of halogen, cyano, -N(SO_2CH_3)$_2$, -SO_2NH_2, halo(C_{1-2})alkyl, C_{1-3}alkoxy;

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, C_{1-2}alkyl, and C_{1-2}alkoxy.

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64. (Original) A compound or salt according to Claim 63, wherein:

R_6 is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -NH(C_{1-4}alkyl), and -N(C_{1-4}alkyl)(C_{1-4}alkyl) and Y; and

Y is independently selected at each occurrence from C_{3-8} cycloalkyl, piperidinyl, piperazinyl,

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tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, and imidazolyl, each of which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio.

60
~~65~~. (Original) A compound or salt according to Claim 58
~~63~~, wherein:

R_9 is cyano, trifluoromethyl, chloro, or iodo; and

R_{9B} is hydrogen.

62 45
~~66~~. (Original) A compound according to Claim ~~50~~, which is

N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

62 45
~~67~~. (Original) A compound according to Claim ~~50~~, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-cyclohexylphenyl)-2-

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methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

68. (Original) A compound according to Claim 45, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl) phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

69. (Original) A compound according to Claim 45, which is (2R)-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

70. (Original) A compound according to Claim 45, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

71. (Original) A compound according to Claim 45, which is (2S)-4-(3-chloropyridin-2-yl)-N-(4-trifluoromethylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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67 45

72. (Original) A compound according to Claim 50, which is (2S)-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

68 45

73. (Original) A compound according to Claim 50, which is (2S)-4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

69 45

74. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(4-piperidin-1-ylphenyl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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70 45

75. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[2-fluoro-4-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

71 45

76. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-[4-(trifluoromethyl)phenyl]-4-[3-

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(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

77. (Original) A compound according to Claim 50, which is (2R)-N-(4-tert-butylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

78. (Original) A compound according to Claim 50, which is (2R)-N-(4-isopropylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

79. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-2,6-dimethyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

80. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2,6-dimethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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76 81. (Original) A compound according to Claim 50, 45 which is 4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2,6-dimethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

77 82. (Original) A compound according to Claim 50, 45 which is (2R)-N-(4-cyclohexylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

78 83. (Original) A compound according to Claim 50, 45 which is 4-(3-chloropyridin-2-yl)-N-(4-cyclohexylphenyl)-2,6-dimethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

Cl

79 84. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-cyclopentylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

80 85. (Original) A compound according to Claim 50, 45 which is (2R)-N-(4-cyclopentylphenyl)-2-methyl-4-[3-

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(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

86. (Cancelled)

87. (Cancelled)

81 88. (Original) A compound according to Claim 50, 45 which is (2R)-N-(4-tert-butylphenyl)-4-(3-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

82 89. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-methoxypyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl] piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

83 90. (Original) A compound according to Claim 50, 45 which is (2R)-N-(4-cyclohexylphenyl)-4-(3-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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91. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

92. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(4-tetrahydro-2H-pyran-4-ylphenyl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

93. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

94. (Original) A compound according to Claim 50, which is (2R)-N-[4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl]-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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88 95. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-(2-methyl-1,3-thiazol-4-yl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

89 96. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(2-ethyl-1,3-thiazol-4-yl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C l

90 97. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(2-methoxy-1,1-dimethylethyl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

91 98. (Original) A compound according to Claim 50, 45 which is (2R)-N-[4-(2-methoxy-1,1-dimethylethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

92 99. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(1-cyano-1-

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methylethyl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

100. (Original) A compound according to Claim 50, which is (2R)-N-[4-(1-cyano-1-methylethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

101. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-ethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

102. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-2-ethyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

103. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-2-ethyl-N-(4-isopropylphenyl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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97 104. (Original) A compound according to Claim 50, 45 which is N-(4-tert-butylphenyl)-2-ethyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

98 105. (Original) A compound according to Claim 50, 45 which is 2-ethyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

99 106. (Original) A compound according to Claim 50, 45 which is 2-ethyl-N-(4-isopropylphenyl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

100 107. (Original) A compound according to Claim 50, 45 which is 2-tert-butyl-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

101 108. (Original) A compound according to Claim 50, 45 which is 2-tert-butyl-N-[4-(trifluoromethyl)phenyl]-4-[3-

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(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

109. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-isopropylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

110. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-2-isopropyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

111. (Original) A compound according to Claim 50, which is 2-isopropyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

112. (Original) A compound according to Claim 50, which is 2-isopropyl-N-(4-isopropylphenyl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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113. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

107

114. (Original) A compound according to Claim 50, 45 which is (2R)-N-(4-tert-butylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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115. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-fluoropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

109

116. (Original) A compound according to Claim 50, 45 which is (2R)-N-(4-cyclohexylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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117. (Original) A compound according to Claim 50, 45 which is (2R)-N-(4-cyclopentylphenyl)-4-(3-fluoropyridin-2-

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yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

118. (Original) A compound according to Claim 50, which is (2R)-N-(4-tert-butylphenyl)-4-(3-cyanopyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

119. (Original) A compound according to Claim 50, which is (2R)-4-(3-cyanopyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

120. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-{4-[cyano(phenyl)methyl] phenyl}-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

121. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[3-methyl-4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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116 122. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-[3-methyl-4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

117 123. (Original) A compound according to Claim 50, 45 which is (2R)-4-{3-[bis(methylsulfonyl)amino]pyridin-2-yl}-N-(4-tert-butylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

118 124. (Original) A compound according to Claim 50, 45 which is (2R)-2-methyl-N-[3-methyl-4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl] piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

119 125. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-{4-[1-(trifluoromethyl)vinyl]phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

120 126. (Original) A compound according to Claim 50, 45 which is (2R)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]-

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N-{4-[1-(trifluoromethyl)vinyl] phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

120 45
127. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-{4-[1-(trifluoromethyl)vinyl] phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

127 45
128. (Original) A compound according to Claim 50, which is (2R)-N-(4-sec-butylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

129 45
129. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-[4-(2,2,2-trifluoro-1-methylethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

130 45
130. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-[4-(2,2,2-trifluoro-1-methylethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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124 131. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloro-5-nitropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

125 132. (Original) A compound according to Claim 50, 45 which is (2R)-4-(5-amino-3-chloropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

126 133. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-fluoropyridin-2-yl)-N-[3-fluoro-4-(trifluoromethyl) phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

127 134. (Original) A compound according to Claim 50, 45 which is (2R)-N-[3-fluoro-4-(trifluoromethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

128 135. (Original) A compound according to Claim 50, 45 which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-

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(2,2,2-trifluoro-1-methylethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

136. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(2,2,4,4-tetrafluoro-4H-1,3-benzodioxin-6-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

137. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-(2,2,4,4-tetrafluoro-4H-1,3-benzodioxin-6-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

138. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-(2,2,4,4-tetrafluoro-4H-1,3-benzodioxin-6-yl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

139. (Original) A compound according to Claim 50, which is (2R)-4-[3-(aminosulfonyl)pyridin-2-yl]-N-(4-tert-butylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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140. (Original) A compound according to Claim 50, which is (2R)-N-(4-benzoylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

141. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-iodophenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

142. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-{4-[2,2,2-trifluoro-1,1-bis(trifluoromethyl)ethyl]phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

143. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-{4-[2,2,2-trifluoro-1,1-bis(trifluoromethyl)ethyl] phenyl}-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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137 144. (Original) A compound according to Claim 45, which is (2R)-N-(4-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

138 145. (Original) A compound according to Claim 45, which is 2-(fluoromethyl)-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

139 146. (Original) A compound according to Claim 45, which is (2R)-N-[4-bromo-3-(trifluoromethyl)phenyl]-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

140 147. (Original) A compound according to Claim 45, which is (2R)-N-[4-bromo-3-(trifluoromethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

141 148. (Original) A compound according to Claim 45, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-fluoro-3-

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(trifluoromethyl) phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

149. (Original) A compound according to Claim 50, which is (2R)-N-[4-fluoro-3-(trifluoromethyl) phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl] piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

150. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl] phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

151. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl) ethyl]phenyl}-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

152. (Original) A compound according to Claim 40, which is (2R)-N-(4-tert-butylphenyl)-4-(3-chloropyrazin-2-

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yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

146 153. (Original) A compound according to Claim 40, 35 which is (2R)-4-(3-chloropyrazin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

147 154. (Original) A compound according to Claim 40, 35 which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

C1

148 155. (Original) A compound according to Claim 40, 35 which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl] phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

149 ~~150~~ 156. (Original) A compound according to Claim 40, 35 which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-{4-cyclopentyl-phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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150 157. (Original) A compound according to Claim 35, which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-{4-cyclohexyl-phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

151 158. (Original) A compound according to Claim 37, which is 4-(3-chloropyridin-2-yl)-N-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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152 159. (Original) A compound according to Claim 37, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

153 160. (Original) A compound according to Claim 37, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[6-(trifluoromethyl)pyridin-3-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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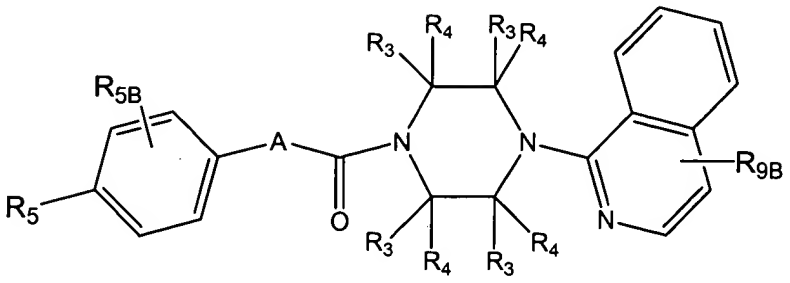
161. (Previously Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_B', $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen [or] and C_{1-6} alkyl;

R_3 and R_4 are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl);

R_5 is selected from the group consisting of halogen, halo(C_{1-6})alkyl, C_{3-6}alkyl substituted with 0-3 R_6, C_{2-6}alkenyl substituted with 0-3 R_6, (C_{3-8}cycloalkyl)C_{1-4}alkyl substituted with 0-3 R_6, and Y;

R_{5B} and R_{9B} each represent from 0 to 2 substituents and are independently chosen from halogen, cyano, nitro,

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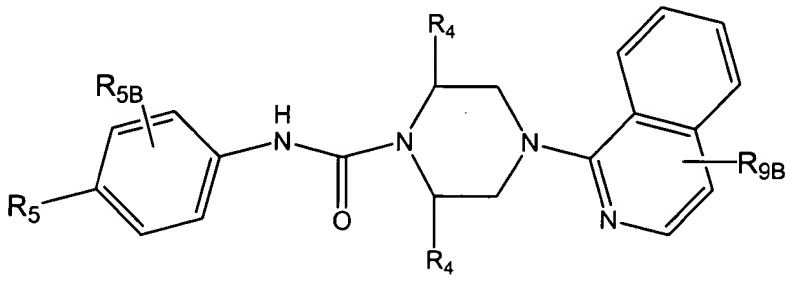
halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy;

R_6 is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl) and Y;

Y is independently selected at each occurrence from C_{3-8} cycloalkyl, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, and imidazolyl, each of which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio.

162. (Original) A compound or salt according to Claim 161 of the Formula:



wherein

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R_4 is independently selected at each occurrence from hydrogen and C_{1-4}alkyl.

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163. (Original) A compound or salt according to Claim 156
162, wherein:

R_5 is selected from the group consisting of halo(C_{1-6})alkyl, C_{3-6}alkyl, (C_{3-8}cycloalkyl)C_{1-4}alkyl, and Y;

R_{5B} and R_{9B} each represent from 0 to 1 substituents and are independently chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy;

Cl

Y is selected from C_{3-8} cycloalkyl, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, and imidazolyl.

157 154
164. (Original) A compound according to Claim 161, which is (2R)-4-isoquinolin-1-yl-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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158 154

165. (Original) A compound according to Claim 161, which is (2R)-N-(4-tert-butylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

159 154

166. (Original) A compound according to Claim 161, which is (2R)-N-(4-isopropylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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160 154

167. (Original) A compound according to Claim 161, which is (2R)-N-(4-cyclopentylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

161 154

168. (Original) A compound according to Claim 161, which is (2R)-N-(4-cyclohexylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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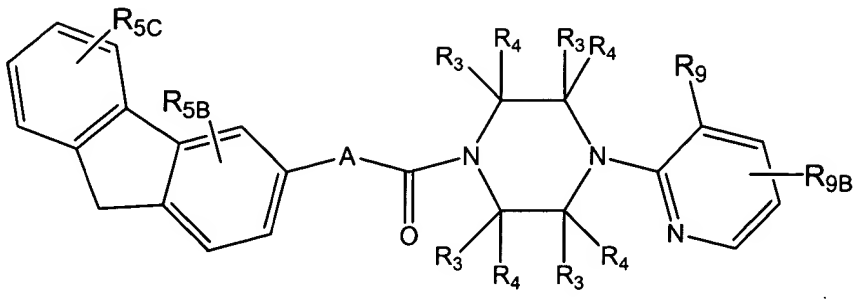
169. (Previously Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_B', $NR_ACR_BR_B'$, $CR_BR_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen and C_{1-6} alkyl;

R_3 and R_4 are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, $-NH(C_{1-6}alkyl)$, and $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$;

R_{5B}, R_{5C}, and R_{9B} each represent from 0 to 2 substituents and are independently chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo(C_{1-3})alkyl, C_{1-3}alkoxy, $-NH(C_{1-3}alkyl)$, and $-N(C_{1-3}alkyl)(C_{1-3}alkyl)$.

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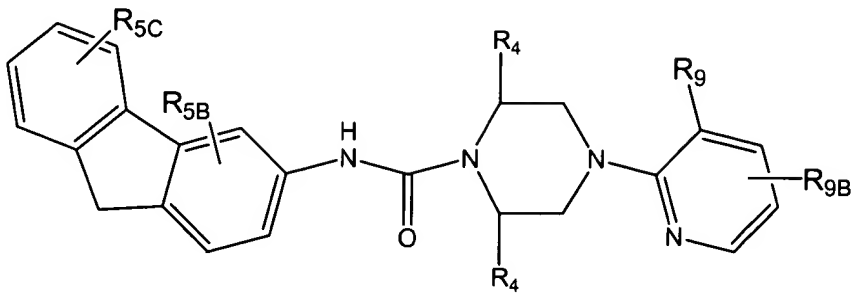
170. (Original) A compound or salt according to Claim 169 of the Formula:



wherein

R_4 is independently selected at each occurrence from hydrogen and C_{1-4}alkyl.

171. (Original) A compound or salt according to Claim 170, wherein:

R_9 is selected from the group consisting of halogen and halo(C_{1-2})alkyl; and

R_{5B} and R_{9B} each represent from 0 to 1 substituents and are independently chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy.

172. (Original) A compound according to Claim 169, which is (2R)-4-(3-chloropyridin-2-yl)-N-(9H-fluoren-2-yl)-

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2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

166 / 173. (Original) A compound according to Claim 169 / 172, which is (2R)-N-(9H-fluoren-2-yl)-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

167 / 174. (Original) A compound according to Claim 33 / 34 / 38, which is (2R)-N-(4-tert-butylcyclohexyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

168 / 175. (Original) A compound according to Claim 33 / 34 / 38, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-isopropylcyclohexyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

169 / 176. (Original) A compound according to Claim 33 / 34 / 38, which is (2R)-N-(4-isopropylcyclohexyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

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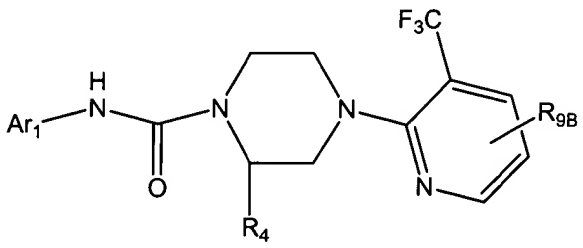
177-192. (Cancelled)

193. (Original) A compound or salt of Claim 50 wherein the compound or salt is not addictive.

194-196. (Cancelled)

197. (Original) A compound of the Formula:



or a pharmaceutically acceptable salt thereof wherein:

R_4 is methyl or hydrogen;

R_{9B} represents 0-2 substituents independently chosen from: halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

Ar_1 is 2,4-dichlorphenyl or 3-nitro-4-chlorophenyl.

198. (Original) A compound of the Formula:

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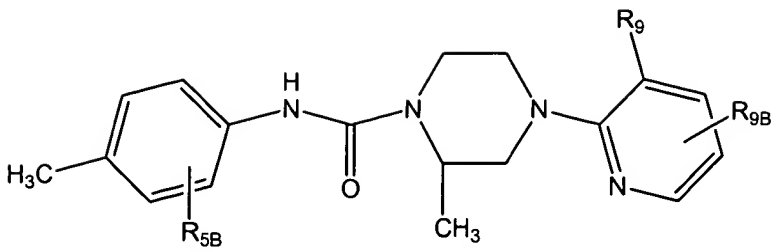

or a pharmaceutically acceptable salt thereof wherein:

R_9 is chloro or trifluoromethyl; and

R_{5B} and R_{9B} independently represent from 0-2 substituents on each of the rings on which they occur and are independently chosen from: halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy.

199. (Previously added) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or salt according to claim 1.

200. (Previously added) A package comprising a pharmaceutical composition of claim 199 in a container and further comprising indicia comprising instructions for using the composition to alleviate pain.

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201. (Previously added) A package comprising a pharmaceutical composition of claim 199 in a container and further comprising indicia comprising instructions for using the composition to alleviate symptoms of exposure to capsaicin or tear gas.

202. (Previously added) A compound or salt of claim 1 wherein, in an *in vitro* assay of capsaicin receptor antagonism, the compound or salt exhibits capsaicin receptor antagonist activity, but in an in vitro assay of capsaicin receptor agonism the compound does not exhibit detectable agonist activity.

203. (Previously added) A compound or salt of claim 1 wherein a dose of the compound or salt that is twice the minimum dose sufficient to provide analgesia in an animal model for determining pain relief does not produce sedation in an animal model assay of sedation.

204. (Previously added) 4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide or a pharmaceutically acceptable salt thereof.

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205. (Previously added) (2R)-N-(4-tert-butylphenyl)-4-[3-(dimethylamino)pyridin-2-yl]-2-methylpiperazine-1-carboxamide or a pharmaceutically acceptable salt thereof.

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206. (Previously added) (2R)-4-[3-(dimethylamino)pyridin-2-yl]-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide or a pharmaceutically acceptable salt thereof.

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207. (Previously added) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or salt according to claim 27.

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208. (Previously added) A compound or salt of claim 27 wherein, in an *in vitro* assay of capsaicin receptor antagonism, the compound or salt exhibits capsaicin receptor antagonist activity, but in an in vitro assay of capsaicin receptor agonism the compound does not exhibit detectable agonist activity.

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209. (Previously added) A compound or salt of claim 27 wherein a dose of the compound or salt that is twice the minimum dose sufficient to provide analgesia in an animal

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model for determining pain relief does not produce sedation in an animal model assay of sedation.

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210. (Previously added) A package comprising a pharmaceutical composition of claim 184 in a container and further comprising indicia comprising instructions for using the composition to alleviate pain.

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211. (Previously added) A package comprising a pharmaceutical composition of claim 184 in a container and further comprising indicia comprising instructions for using the composition to alleviate symptoms of exposure to capsaicin or tear gas.

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